HH25524

Reviewer: S. Semalulu Date: April 10, 2001

STUDY TYPE: Sub-chronic Oral Toxicity [feeding - dog]; OPPTS 870.3150 (non-rodent) [§82-1]; OECD 409.

TEST MATERIAL (PURITY): SZX 0722 (99.4%) [Iprovalicarb]

SYNONYMS: Melody

CITATION: M. Vliegen and E. Hartmann (1995): SZX 0722 - Sub-chronic toxicity in dogs (13-week study by oral administration). Bayer AG, report no. 24337 (October 04, 1995). Unpublished.

SPONSOR: Bayer Corporation.

EXECUTIVE SUMMARY:

In a sub-chronic toxicity study (MRID not available), beagle dogs (4/sex/group) were fed diets containing technical SZX 0722 (95.8 %) at doses of 0, 250, 2500, or 50000 ppm (9.1, 62.5 or 1250 mg/kg bw/day for both sexes), for 13 weeks. Four dogs in the 50000 ppm dose group were described as being skinny. One female of the 50000 ppm group was killed in extremis four weeks prior to study termination. Decreases in food consumption and body weight gain occurred in both sexes at 50000 ppm. Plasma protein, especially albumin was decreased in both sexes at 2500 ppm and markedly decreased in 50000 ppm dose group. Alkaline phosphatase (ALP) activity was slightly, and markedly elevated at 2500, and 50000 ppm respectively. The activities of AST, ALT and GLDH were distinctly increased at 50000 ppm. Serum LDH activity was slightly increased at the end of the study, at 50000 ppm. A decrease in cholesterol level was seen at 50000 ppm. The absolute and relative liver weights were increased in all dogs at 2500 ppm and above. The absolute prostate weight was deceased in 2/4 dogs at 2500 ppm and in 4/4 males at 50000 ppm. Absolute testes weights were decreased in 4/4 males at 50000 ppm, and absolute thymus weights were decreased in 2/3 females and 3/4 males at 50000 ppm. Treatment-related discolouration and distinct lobulation of the liver occurred most frequently in males at $\geq$ 2500 and 50000 ppm, and in one female at 50000 ppm. Abnormal contents of the gall bladder were observed at 50000 ppm. Hepatocellular hypertrophy, multi lamellar bodies, and granulocytic infiltration were observed in one or more animals of either sex at 2500 ppm and above. In addition, dogs at Hepatocyte cytoplasmic vacuolation, focal hepatic necrosis, and iron containing pigments (hemosiderin) within peri-portal hepatocytes and Kupffer cells were noted in dogs at 50000 ppm. The presence of a generalised atrophy of fatty tissues with dilatation and edema of the lymphatic vessels, and serous atrophy of femoral and sternum bone marrow, and decreased absolute testes and prostate weights at 50000 ppm were attributed to the very poor physical condition of the dogs rather than a specific organ/tissue toxicity response. The microsomal enzymes N-Demethylase (N-DEM) and O-Demethylase (O-DEM) and cytochrome P-450 were increased at $\geq$ 250 ppm. The elevation of liver microsomal enzyme at 250 ppm was considered and adaptive response resulting from enzyme induction rather than an adverse effect. The LOAEL was 2500 pmm (62.5 mg/kg bw/d), based on increased absolute and relative weight, hepatocellular hypertrophy, increased serum activity of alkaline phosphatase, decreased plasma protein levels). The NOAEL in both sexes was 250 ppm (9.1 mg/kg bw/day).

This sub-chronic toxicity study is classified acceptable and satisifies guideline requirements (409) for a

short term toxicity study in dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

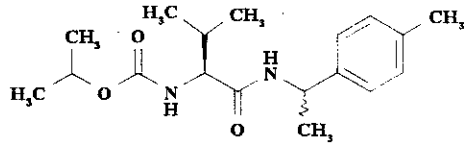
I. MATERIALS AND METHODS

A. MATERIALS:

1 **Test Material:** SZX 0722

Description:	Technical, white solid lumps or powder
Lot/Batch #:	05013/0194.
Purity:	95.8 % a.i.
Compound Stability:	Stable at room temperature
CAS #:	

Structure



2. **Vehicle and/or positive control:** not applicable

3 **Test animals:**

Species:	Canine	
Strain:	Purebred Beagle (Bor:Beag strain)	
Age/weight at study initiation	19-23 weeks old, 6.0 to 8.9 kg	
Source:	F. Winklelmann Breeders, Brechen	
Housing:	Individual stainless steel cages in climate controlled rooms	
Diet:	Ssniff HH Sole Diet for Dog Maintenance *(Ssniff Versuchstierdiete,GmbH, D-59480Soest)*	
Water:	Tap water provided *ad libitum*	
Environmental conditions:	**Temperature:**	20.0-23.0° C
	Humidity:	3–50 %
	Air changes:	n/a
	Photo period:	12 hrs dark/ 12 hrs artificial light
Acclimation period:	14 days	

B. STUDY DESIGN:

1. **In life dates** - July 1994 - October 1994.

2. **Animal assignment**: Animals were assigned randomly to the test groups noted in Table 1.

TABLE 1: Study design

Test Group	Conc. in Diet (ppm)	Average dose (mg/kg bw/day)	Number of animals/ dose group	
		male and female	Male	Female
Control	0	0.0	4	4
Low	250	9.1	4	4
Mid	2500	62.5	4	4
High	50000	1250	4	4

3. Diet preparation and analysis

Test diets were prepared fresh weekly by mixing appropriate amounts of test substance with basal diet and were stored at ambient temperature . Homogeneity and stability were tested on samples of food from every batch of test and control diet prepared and were analysed by HPLC for stability and concentration. Determination of SZX 0722 content was made on samples of feed from each concentration prepared.

Results - Homogeneity Analysis: 98.9 to 104% of nominal concentration

Stability Analysis: -96% to 113% , stable for 14 days at ambient temperature.

Concentration Analysis: range 87.6% to + 91.8 % of nominal concentration.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage did not exceed 15%.

4. Statistics - Given the small number of animals per group, only descriptive statistics were performed, including calculations of arithmetical means and standard deviation. Body weights, food consumption, and organ weights were analysed by comparing each dose level to the control, using Dunnett's test. The statistical methods used were acceptable.

C. METHODS:

1. Observations:

Thorough physical examinations were conducted on all animals at pretreatment and just before termination. The animals were inspected twice daily for signs of toxicity and mortality.

2. Body weight:

Animals were weighed weekly from day -7 up to study termination.

3. Food consumption and compound intake:

Food consumption for each animal was determined each day Food efficiency (body weight gain in kg/food consumption in kg per unit time X 100) was not provided. Compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. Ophthalmoscopic examination:

Eyes of all animals were examined at pre-treatment and just before termination

5. Haematology & Clinical Chemistry:

Blood was collected at 6 and 13 weeks of treatment, for haematology and clinical analysis from all surviving animals. The parameters CHECKED (X) in the table below were examined.

a. Haematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpuscular. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpuscular. volume (MCV)
x	Platelet count*	x	Reticulocyte count
x	Blood clotting measurements*		
x	(Thromboplastin time)		
x	(Thromboplastin time)		
x	(Clotting time)		
x	(Prothrombin time)		

* Required for sub-chronic studies based on Subdivision F Guidelines

b. Clinical Chemistry

X	**ELECTROLYTES**	X	**OTHER**
	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
x	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*	x	Total Cholesterol
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
		x	Total bilirubin
	ENZYMES	x	Total serum protein (TP)*
x	Alkaline phosphatase (ALP)	x	Triglycerides
x	Cholinesterase (ChE)	x	Serum protein electrophores
x	Creatine phosphokinase		
x	Lactic acid dehydrogenase (LDH)		
x	Serum alanine amino-transferase (ALT)*		
x	Serum aspartate amino-transferase (AST)*		
x	Gamma glutamyl transferase (GGT)		
x	Glutamate dehydrogenase (GLDH)		

* Required for sub-chronic studies based on Subdivision F Guidelines

6. Urinalysis*

Urine was collected from fasted animals, at 6 and 13 weeks of treatment, and the parameters checked (x) in the table below were examined.

X		X	
x	Appearance	x	Glucose
x	Volume	x	Ketones
x	Specific gravity	x	Bilirubin
x	pH	x	Blood
x	Sediment (microscopic)	x	Nitrate
x	Protein	x	Urobilinogen

* Not required for sub-chronic studies

7. Sacrifice and Pathology

All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the tissues CHECKED (X) were collected for histological examination. The organs checked (XX), in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
x	Tongue	x	Aorta*	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)^{T}
x	Stomach*	x	Lymph nodes*	x	Eyes (optic n.)^{T}
x	Duodenum*	xx	Spleen*		
x	Jejunum*	x	Thymus*		GLANDULAR
x	Ileum*			xx	Adrenal gland*
x	Cecum*		UROGENITAL	x	Lacrimal gland^{T}
x	Colon*	xx	Kidneys*+	x	Mammary gland^{T}
x	Rectum*	x	Urinary bladder*	xx	Parathyroids*+-
xx	Liver*+	xx	Testes*+	xx	Thyroids*+-
x	Gall bladder*	x	Epididymides	xx	Pituitary*
x	Pancreas*	x	Prostate		
		x	Seminal vesicle		OTHER
	RESPIRATORY	xx	Ovaries		Bone
x	Trachea*	x	Uterus*		Skeletal muscle
x	Lung*				Skin
x	Nose				All gross lesions and masses*
x	Pharynx				
x	Larynx				

* Required for sub-chronic studies based on Subdivision F Guidelines xx = Organ weighed.

II. RESULTS

A. Observations :

1. Clinical signs of toxicity -

Emesis was observed sporadically across the test and control groups. Repeated instances of incomplete (decreased) food consumption were observed in animals at 50000 ppm. This was considered treatment-related, as it was associated with reduction in body weight gain at that dose level.

2. Mortality -
One female dog in the 50000 ppm dose group was killed because of its poor body condition.

B. Body weight and weight gain:
Average body weight and body weight gain data are presented in Table 2, and Figure 1. Consistently reduced body weight compared to controls, occurred in all animals (combined by sex), at 50000 ppm, throughout most of the study period. The body weight reduction was considered a treatment related adverse effect.

TABLE 2. Average body weights (kg) in male and females combined, during 13 weeks of treatment

	0 ppm	250 ppm	2500 ppm	50000 ppm
Week	(n=8)	(n = 8)	(n=8)	(n=7-8)
-2	7.5± 0.08	7.4 ± 0.6	7.6 ± 0.8	7.3 ± 0.6
-1	7.4 ± 0.92	7.5 ± 0.6	7.6 ± 0.9	7.3 ± 0.6
1	7.5 ± 0.95	7.7 ± 0.5	7.8 ± 0.7	7.3 ± 0.5
2	7.8 ± 1.0	7.9 ± 0.6	8.0 ± 0.8	7.4 ± 0.6
3	8.1 ± 1.0	8.0 ± 0.6	8.1 ± 0.8	7.3 ± 0.6
4	8.2 ± 1.0	8.2 ± 0.5	8.2 ± 0.9	7.2 ± 0.7
5	8.2 ± 1.0	8.3 ± 0.6	8.4 ± 0.9	7.1 ± 0.8
6	8.3 ± 1.0	8.4 ± 0.6	8.4 ± 0.9	7.0 ± 0.8
7	8.5 ± 1.0	8.4 ± 0.7	8.7 ± 0.8	7.0 ± 0.9
8	8.5 ± 1.2	8.5 ± 0.7	8.7 ± 0.8	6.8 ± 0.9
9	8.6 ± 1.3	8.6 ± 0.7	8.7 ± 0.8	6.9 ± 0.9
10	8.7 ± 1.2	8.7 ± 0.7	8.8 ± 0.9	6.7 ± 1.3
11	8.6 ± 1.3	8.6 ± 0.8	8.7 ± 0.9	7.0 ± 1.0
12	8.8 ± 1.3	8.6 ± 0.8	8.7 ± 0.9	7.0 ± 0.1
13	9.0 ± 1.3	8.8 ± 0.8	8.9 ± 0.9	7.1 ± 1.2
14	8.9 ± 1.4	8.4 ± 0.9	8.6 ± 0.9	6.8 ± 1.1

[a] Data obtained from page 161 in the study report.

C. Food consumption and compound intake:

1. Food and water consumption -

Mean food consumption data was presented by the day (page 87-108 in study report) and not summarised by the week. Statistical analysis of the food consumption data (page numbers 79 - 86 in study report) indicates significantly reduced ($p < 0.01$) food consumption for both sexes, at 50000 ppm, throughout most of the study duration. The reduction in food consumption at 50000 ppm, was accompanied by notable reduction in body weight gain, and was considered a treatment related. Water intake was not affected by treatment.

2. Compound consumption The calculated compound intake (mg/kg bw/day) is presented in Table 1 -

3. Food efficiency

Food efficiency data were not provided.

D. Ophthalmoscopic examination -

There were no treatment-related opthalmological effects.

E. Blood analyses

1. Haematology

There were no treatment-related hematological findings.

2. Clinical Chemistry - Clinical chemistry findings are presented in Table 3.

The activities of serum enzymes; aspartate amino-transferase (AST), alanine amino-transferase (ALT) and glutamate dehydrogenase (GLDH) were distinctly increased at 50000 ppm. Lactic acid dehydrogenase (LDH) activity was slightly increased in that dose-group, but only at the end of the treatment period (week 13). Alkaline phosphatase (ALP) activity was slightly elevated at 2500 ppm and markedly elevated at 50000 ppm. Cholesterol level was distinctly decreased in dogs of the 50000 ppm-groups. Plasma protein levels in general and albumin in particular, were decreased at 2500 and above. These changes were considered related to toxic events in the liver.

F. Urinalysis

Urinalysis parameters were not affected by treatment.

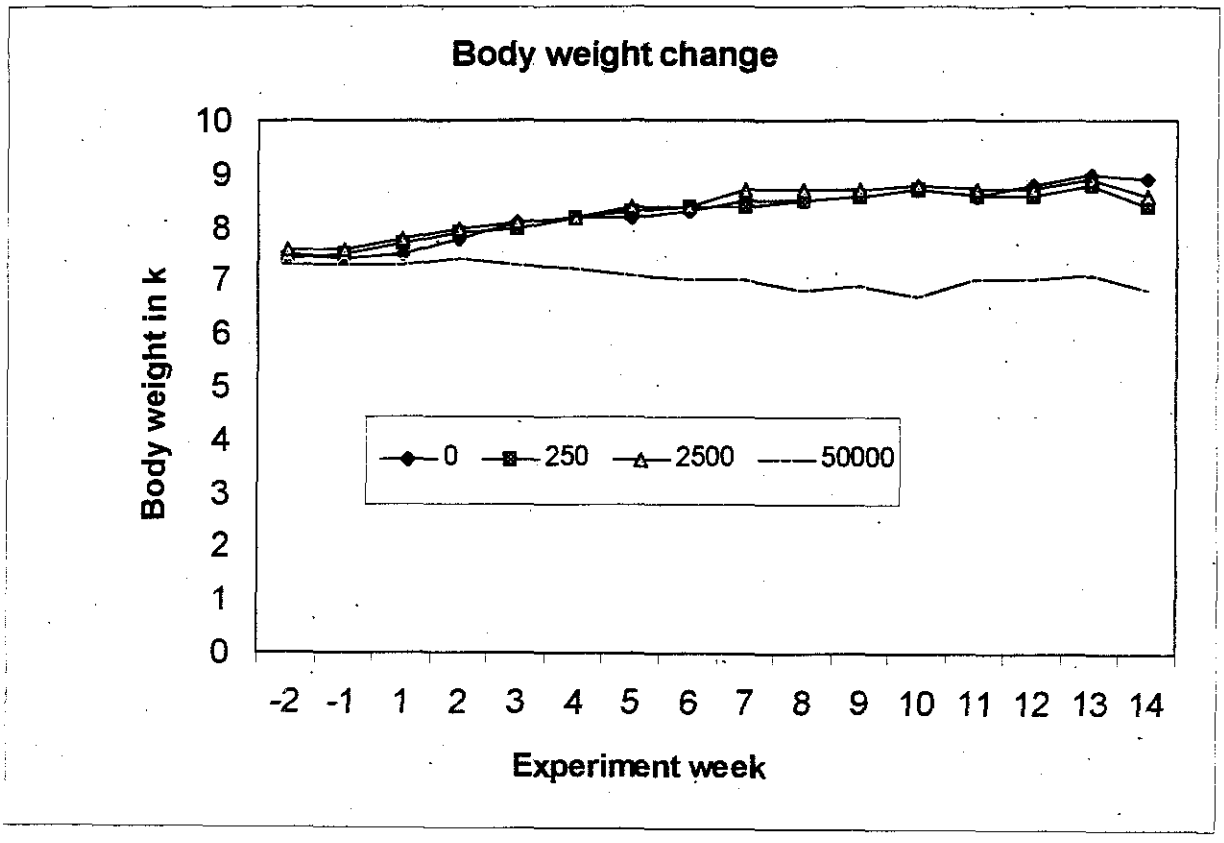


Figure 1. Effect on body weight.

Table 3. Clinical chemistry ; mean values pooled for male and female animals.

	0 ppm			250 ppm			2500 ppm			50000 ppm		
week	**-2**	**6**	**13**	**-2**	**6**	**13**	**-2**	**6**	**13**	**-2**	**6**	**13**
AST [U/l]	16.2	13.2	16.2	14.4	12.5	13.8	14.1	12.7	12.8	12.8	27.7	41.0
ALT [U/l]	22.1	17.3	16.7	19.6	17.0	26.6	19.3	17.6	23.9	22.0	133.4	272.8
GLDH [U/l]	3.7	2.4	1.5	4.1	2.5	1.0	3.1	2.3	1.2	3.6	22.4	77.0
ALP [U/l]	258	196	192	237	217	217	261	355	345	204	456	759
LDH [U/l]	48	40	50	47	32	41	44	33	43	44	49	72
CHOL[mmol/l]	2.97	3.52	3.60	3.57	3.65	3.66	3.78	3.22	3.37	3.50	1.07	0.95
PROT [g/l]	59.7	60.6	62.2	59.7	57.9	58.5	61.1	55.9	55.5	59.5	47.6	48.2
ALB [g/l]	-	33.3	35.5	-	31.5	32.0	-	29.5	29.4	-	22.3	20.6

G. Microsomal liver enzymes

Microsomal liver enzymes (N-demethylase and O-demethylase) were induced by SZX 0722- treatment at 250 ppm and 2500 ppm, but the increase declined slightly at 50000 ppm. Triglycerides were slightly increased at 250 and above, but to a slight extent at the highest dose. This was interpretable as a physiological mobilisation of storage lipids rather than an adverse effect. The slight decline serum protein levels at 50000 ppm was interpreted as a treatment-related liver effects which resulted in the restriction of synthesis performance of the liver. Cytochrome P-450 content however remained elevated in a dose-related fashion from $\geq$ 250 ppm.

Table 4. Microsomal enzyme, and triglyceride levels in liver tissue

	0 ppm	250 ppm	2500 ppm	50000 ppm
week	**14**	**14**	**14**	**14**
N-DEM [mU/g]	87.5	226.0	303.0	223.8
O-DEM [mU/g]	23.2	44.9	58.2	38.0
P-450 [nmol/g]	19.5	41.3	62.8	67.3
TRIGL [mcmol/g]	4.26	5.97	9.45	6.22

G. <u>Sacrifice and Pathology:</u>

1. Gross pathology.

The physical bod status of all 4/4 male dogs in the 50000 ppm dose group was judged to be skinny. The prostates of 4/4 males and testes in 2/4 males at 50000 ppm were diminished in size. The thymus of 3/4 males at 50000 ppm and 1/4 males at 250 ppm were decreased in size compared to controls. The changes in size of prostate, testes and thymus at 50000 ppm were considered treatment related, possibly attributable to the extensive wasting at that dose. Discolouration and distinct lobulation of liver was noted in all treated

groups. Changes in the gall bladder contents were recorded most frequently at 50000 ppm. The gross changes seen in the liver at 250 ppm were not considered toxicologically significant as it was not accompanied by histological alterations or liver enzyme changes.

2. Organ weight -

Results of organ weights are summarized in Table 5. Absolute thymus weights were decreased in 2/3 females and 3/4 males at 50000 ppm. The significant decreases in absolute thymus and testes weights at 50000 ppm, and a decrease in absolute prostate weight at ≥ 2500 ppm were considered treatment-related. Absolute and relative liver weights were increased at 250 ppm and above. The relative liver weight increase at 2500 ppm and 50000 ppm was considered a toxicologically significant treatment related effects due to accompanying histological changes in the liver and changes in serum liver enzyme activities. The relative liver weight increase at 250 ppm was considered an adaptive response rather than an adverse effect because there were no accompanying changes in liver histology or serum liver enzyme activities.

Table 5. Organ weights changes.

	0 ppm	250 ppm	2500 ppm	50000 ppm
Males and females				
number of animals	**8**	**8**	**8**	7
abs. liver weight (g)	320	360	426	419
rel. liver weight (g/kg bw)	36	43	50	61
abs. thymus weight	8	8.4	7.6	3.4
rel. thymus weight	0.9	1	1	0.4
males (n = 4)				
number of animals	**4**	**4**	**4**	**4**
abs. testes weight (g)	12.6	16.2	15	4.4
rel testes weight g/kg bw	1	2	2	1
abs. prostate weight	2.3	2.1	1.8	0.8

3. Microscopic pathology

Treatment-related increased incidences of hepatocellular hypertrophy, vacuolation, single cell necrosis as well as focal hepatic necrosis, multi lamellar bodies in hepatocytes, granulocytic infiltration and iron positive pigment in hepatocytes and Kupffer cells, were observed in at least one animal of either sex at 2500 ppm and in most animals at 50000 ppm. There was also edema and dilatation of lymphatic vessels of the gall bladder, atrophy of lymphatic tissue, atrophy of adipose tissue of the tongue and sub-cutis, and serous atrophy of femoral and sternum bone marrows, and decreases in prostate and testes weights at 50000 ppm.

III. DISCUSSION

Administration of SZX 0722 in the diet was well tolerated at a dose level of 250 ppm (9.1 mg/kg bw/d) during the 13-week treatment period. The slightly elevated relative liver weights, accentuated lobulation pattern of the liver and increase of microsomal enzyme (N-DEM, O-DEM and P-450, cytoplasmic changes,) at 250 ppm were attributed to enzyme induction and were regarded as an adaptive, rather than an adverse effect. The generalised atrophy of fatty tissues (lymphatic tissues, subcutis, tongue, bone marrow and testes and prostate) at 50000 ppm was attributable to the general poor physical body condition of the animals, rather than a direct tissue/organ toxic effect. Microsomal liver enzymes (N-demethylase and O-demethylase) were induced by SZX 0722- treatment at 250 ppm and 2500, but declined slightly at 50000 ppm. The decline in levels of these enzymes at 50000 ppm can be interpreted as a consequence of the hepatotoxicity at this dose-level as the synthesis performance of the liver is already restricted. Cytochrome P-450 content however remained elevated at 250 ppm and above.

A. Investigators' conclusions:

The LOAEL was 2500 pmm, based on the liver effects (increased absolute and relative liver weight, increased activity of alkaline phosphatase levels, hepatocellular hypertrophy and vacuolation), decreased plasma albumin levels, and decreased in absolute prostate weight at 2500 ppm. The NOAEL was 250 ppm (9.1 mg/kg bw/day for males and females).

B. Reviewer comments:

I concur with the study authors conclusions. The LOAEL was 2500 ppm (62.5 mg/kg bw/d), based on increases in absolute and relative liver weights, increased activity of alkaline phosphatase levels, hepatocellular hypertrophy and vacuolation, decreased plasma albumin levels, and decreased in absolute prostate weight at that dose. The NOAEL was 250 ppm (9.1 mg/kg bw/day for both sexes).

C. Study deficiencies:

There were no deficiencies that would affect the acceptability of this study.

IPROVALICARB

Subchronic (13-week) dietary study in dogs: **MRID No. 44865714**

Week 13 Body Weights for Dogs
(refer to body weight table [combined sexes] DER p. 6

Week	males (kg) - ppm				females (kg) - ppm			
	0	250	2500	50000	0	250	2500	50000
-1	7.9	7.8	8.0	7.5	7.0	7.2	7.2	7.1
1	8.0	7.8	8.0	7.4	7.1	7.6	7.5	7.2
4	8.6	8.16	8.5	7.3	7.6	8.2	7.9	7.1
8	9.0	8.5	9.0	6.8	8.0	8.5	8.4	6.9
14	9.3	8.2	8.9	6.6	8.4	8.6	8.3	7.0a
WT chg: -1 to 14	+1.4	+0.4	+0.9	-0.9	+1.4	+1.4	+1.1	-0.1

WT chg: = weight change
number of dogs/sex/group = 4 (see exception below)
a = mean of 3 dogs; one dog died day 68 (week 10); began losing weight week 6.
Data extracted from Report page 160.

IPROVALICARB

Subchronic (13-week) dietary study in dogs: **MRID No. 44865714**

Selected Week 13 Organ Weights for Dogs
(refer to organ weight table [combined sexes] DER p. 10.

Organ	males (ppm)				females (ppm)			
	0	250	2500	50000	0	250	2500	50000
F BW - kg	9.3	8.2	8.9	6.6	8.4	8.6	8.3	6.5a
absol. liver - g	337	397	357	420	303	324	396	417
rel. liver - g/kg	36	49	52	62	36	38	48	59e
absol. thymus - g	6.5	9.5	6.5	2.2c	9.5	10.3	8.5	5.0d
rel. thymus - g/kg	0.8	0.8	1.0	0.3	1.0	1.3	1.0	0.7d

number of dogs/sex/group
F BW = final body weight
a = includes one dog that died day 68 (week 10).
b = does not include liver (133 g) from dog that died; other livers weighed 416, 489 and 349 g.
c = individual weights = 1.0, 5.0, 2.0 and 0.6 g.
d = thymus of dog that died not weighed.
e = dies not include liver (28 g/kg) from dog that died.
Data extracted from Report page 238.

SEE MICROSCOPIC PATHOLOGY DER P.10

PATHOLOGY REPORT : MRID 44865714 PAGE : 10
T 7055539

TEST ARTICLE : SZX 0722 PATHOL. NO.: 04353 HAR
TEST SYSTEM : BEAGLE, 13 WEEKS, FEEDING DATE : 24-JUL-95
SPONSOR : BAYER AG PATHDATA SYSTEM V3.5d

EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL

M	= MALE ANIMAL
F	= FEMALE ANIMAL
K0	= TERMINAL SACRIFICE GROUP
+	= INTERCURRENT DEATH/SACRIFICED MORIBUND

CODES AND SYMBOLS USED AT ORGAN LEVEL:

G	= GROSS OBSERVATION CHECKED OFF HISTOLOGICALLY
!	= GROSS OBSERVAT.NOT CHECKED OFF HISTOLOGICALLY
0	= TISSUE NOT PRESENT FOR HISTOLOGIC EXAMINATION
'	= HISTOLOGIC EXAMINATION NOT REQUIRED
+	= ORGAN EXAMINED, FINDINGS PRESENT
-	= ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
(	= ONLY ONE OF PAIRED ORGANS EXAMINED/PRESENT

CODES AND SYMBOLS USED AT FINDING LEVEL:

GRADE 1	= MINIMAL / VERY FEW / VERY SMALL
GRADE 2	= SLIGHT / FEW / SMALL
GRADE 3	= MODERATE / MODERATE NUMBER / MODERATE SIZE
GRADE 4	= MARKED / MANY / LARGE
GRADE 5	= MASSIVE / EXTENSIVE NUMBER / EXTENSIVE SIZE
P	= FINDING PRESENT, SEVERITY NOT SCORED
(	= FINDING UNILATERAL IN PAIRED ORGANS

1

4.

PATHOLOGY REPORT : PAGE : 11
SUMMARY TABLES T 7055539

TEST ARTICLE : SZX 0722 PATHOL. NO.: 04353 HAR
TEST SYSTEM : BEAGLE, 13 WEEKS, FEEDING DATE : 24-JUL-95
SPONSOR : BAYER AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. +

	DOSE GROUP:	01		02		03		04	
	SEX:	M	F	M	F	M	F	M	F
ORGAN/FINDING	NO.ANIMALS:	4	4	4	4	4	4	4	4
HEART	NO.EXAM.:	4	4	4	4	4	4	4	4
- FOC.AORTIC CALCIFIC.		1							
LUNGS	NO.EXAM.:	4	4	4	4	4	4	4	4
- ACC.MACROPHAGES		2			2			3	1
- SEPTAL THICKENING		1				1			1
- GRANULOMA								1	
- PLEURITIS FOCAL						1			
- ALV.FIBRIN						1			
- ROUND CELL INFILTR.		1	1	2	2	1	1		2
- GRANULOCYT.INFILTR.		2							
- EMPHYSEMA					1				1
TONGUE	NO.EXAM.:	4	4	4	4	4	4	4	4
- ATROPHY ADIPOSE TIS.								1	1
- FOCAL INFLAMMATION			2	1	4	1	1	3	1
ESOPHAGUS	NO.EXAM.:	4	4	4	4	4	4	4	3
- LYMPHOCYTIC INFILTR.					1	1			
STOMACH	NO.EXAM.:	4	4	4	4	4	4	4	4
- MICROEROSION				1					
- GIANT CELLS		1	1	2	1	3		1	
- LYMPH FOLLICLES			1	1	1	2		2	3
INTESTINE	NO.EXAM.:	4	4	4	4	4	4	4	4
- HYPEREMIA					1				
- VACUOLATION PP				1					
- DILATED CRYPTS									1

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TEST ARTICLE : SZX 0722 PATHOL. NO.: 04353 HAR
TEST SYSTEM : BEAGLE, 13 WEEKS, FEEDING DATE : 24-JUL-95
SPONSOR : BAYER AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. +

DOSE GROUP:		01		02		03		04	
SEX:		M	F	M	F	M	F	M	F
ORGAN/FINDING	NO.ANIMALS:	4	4	4	4	4	4	4	4
LIVER	NO.EXAM.:	4	4	4	4	4	4	4	4
- CYTOPLASMIC CHANGE				3	2	3	4	4	3
- CYTOPLASM.VACUOLAT.								1	2
- HEPATOCELL.HYPERTR.							1	2	3
- FOCAL NECROSIS					1			3	1
- HEMOSIDERIN HEPATOC,								3	1
- HEMOSIDERIN KUPFFER.								2	3
- MULTILAMELLAR BODIES							1	1	2
- SINGLE CELL NECROSIS								4	2
- GRANULOCYTIC INFIL.						1		3	1
- CYTOPL.INCL./VAC.		1	1				2		
- ROUND CELL INFILTR.			1					2	
- KUPFFER CELL PROL.			1				1	1	2
- CONGESTION						1		1	
LIVER (ORO)	NO.EXAM.:	4	4	4	4	4	4	4	4
- FATTY CHANGE				2	1	1	2		1
GALLBLADDER	NO.EXAM.:	4	4	4	4	4	4	4	3
- EDEMA WALL			1	1	1	1	1	4	3
- DILATED LYMPH.VESSEL				1		1	1	4	2
- BROWN MATERIAL LUMEN								3	2
- LYMPHOCYTIC INFILTR.		3	3	4	3	4	4	3	2
PANCREAS	NO.EXAM.:	4	4	4	4	4	4	4	4
- APOPTOTIC BODIES		3	2	1	3	2	2	2	1
- ATROPHY									1
- FIBROSIS			1						
KIDNEYS	NO.EXAM.:	4	4	4	4	4	4	4	4
- TUBULAR DEGENERATION								1	
- BASOPHILIC TUBULES								1	
- DILATED TUBULES								1	
- ROUND CELL INFILTR.			1		2		1	1	1
- CASTS HENLE'S LOOP		2	2	4	3	1	1	1	1
- CELLULAR DEBRIS			1						
- VACUOL.TUBULAR CELLS						1			

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TEST ARTICLE : SZX 0722 PATHOL. NO.: 04353 HAR
TEST SYSTEM : BEAGLE, 13 WEEKS, FEEDING DATE : 24-JUL-95
SPONSOR : BAYER AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. +

	DOSE GROUP:	01		02		03		04	
	SEX:	M	F	M	F	M	F	M	F
ORGAN/FINDING	NO.ANIMALS:	4	4	4	4	4	4	4	4
TESTES	NO.EXAM.:	4		4		4		4	
- HYPOPLASTIC TUBULES		1		1		1			
- SPERMAT.GIANT CELLS		1		1					
- JUVENILE		1				1		4	
EPIDIDYMIDES	NO.EXAM.:	4		4		4		4	
- REDUCED SPERM CONT.		1							
- SPERMATIDS		1		1		1			
- FOCAL HYPOPLASIA						1			
- JUVENILE		1				1		4	
PROSTATE	NO.EXAM.:	4		4		4		4	
- JUVENILE		1		1		1		4	
OVARIES	NO.EXAM.:		4		4		4		4
- CYST							1		
- JUVENILE			1						1
PITUITARY GLAND	NO.EXAM.:	4	4	4	4	4	4	4	4
- CYST(S)			1	1	2		1	1	1
THYROID GLAND	NO.EXAM.:	4	4	4	4	4	4	4	4
- COLLOIDAL VACUOLAT.			1		2				1
- CYSTIC FOLLICLE		1	1	1				1	1
- C-CELL AGGREGATION			2	1	1				1
PARATHYROID GLANDS	NO.EXAM.:	4	4	4	4	4	4	4	3
- CYST(S)			1		1		1		
ADRENAL GLANDS	NO.EXAM.:	4	4	4	4	4	4	4	4
- VACUOLES Z.GLOM.			1			3		1	
- VACUOLES Z.FASCICUL.				2				1	1
- CYST		1							

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TEST ARTICLE : SZX 0722 PATHOL. NO.: 04353 HAR
TEST SYSTEM : BEAGLE, 13 WEEKS, FEEDING DATE : 24-JUL-95
SPONSOR : BAYER AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. +

DOSE GROUP:	01		02		03		04	
SEX:	M	F	M	F	M	F	M	F
ORGAN/FINDING NO.ANIMALS:	4	4	4	4	4	4	4	4
SPLEEN NO.EXAM.:	4	4	4	4	4	4	4	4
- LYMPHATIC ATROPHY							2	1
- HEMOSIDERIN								1
- CONGESTION				2			1	
BONE MARROW NO.EXAM.:	4	4	4	4	4	4	4	4
- SEROUS ATROPHY							3	1
- HYPEREMIA								1
- LYMPHFOLL.LIKE STR.					1	1		
TONSILS NO.EXAM.:	4	4	4	4	4	4	4	4
- INFLAMMATION	2	4	4	4	4	4	4	4
THYMUS NO.EXAM.:	4	4	4	4	4	4	4	3
- ATROPHY							4	2
- CYST(S)	1	1						
- BLOOD		1						
MESENT. LYMPH NODE NO.EXAM.:	4	4	4	4	4	4	4	4
- LYMPHATIC ATROPHY								1
MANDIB.LYMPH NODES NO.EXAM.:	4	4	4	4	4	4	4	4
- LYMPHATIC ATROPHY								1
LYMPH NODES NO.EXAM.:								1
- LYMPHADENITIS(PANCR)								1
SALIVARY GLANDS NO.EXAM.:	4	4	4	4	4	4	4	4
- ROUND CELL INFILTR.				1				
PAROTID GLAND NO.EXAM.:	4	3	4	4	4	4	4	4
- ROUND CELL INFILTR.			1					
SKIN(MAMMARY GLAND) NO.EXAM.:	4	4	4	3	4	4	4	4
- ATROPHY ADIPOSE TIS.							2	1
- FOC.INFLAMMATION		1		1		1	1	

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TEST ARTICLE : SZX 0722 PATHOL. NO.: 04353 HAR
TEST SYSTEM : BEAGLE, 13 WEEKS, FEEDING DATE : 24-JUL-95
SPONSOR : BAYER AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. +

DOSE GROUP:	01		02		03		04	
SEX:	M	F	M	F	M	F	M	F
ORGAN/FINDING NO.ANIMALS:	4	4	4	4	4	4	4	4
SKELETAL MUSCLE NO.EXAM.:	4	4	4	4	4	4	4	4
- ATROPHY								1
- FOC.FIBER DEGENER.								1
FEMUR NO.EXAM.:	4	4	4	4	4	4	4	4
- SEROUS ATROPHY							1	1
STERNUM NO.EXAM.:	4	4	4	4	4	4	4	4
- SEROUS ATROPHY							1	1
EYES NO.EXAM.:	4	4	4	4	4	4	4	4
- CONJUNCTIVITIS								1

END OF REPORT SECTION

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